**A Clinical Guideline for Administration of Tacrolimus in Adults Nil-By-Mouth (NMB) Renal Patients**

**Aim and purpose of guideline**

To provide recommendations and guide safe practice for the prescribing and monitoring of Tacrolimus for adult renal transplant patients who are nil-by-mouth (NBM) or who cannot take medications orally. This guideline applies to all renal inpatient admitted across University Hospitals Sussex with the exception of renal patients admitted to St Richard’s Hospital who are under the care of Wessex Kidney Unit – Portsmouth.

**Introduction**

Tacrolimus is a highly potent immunosuppressive agent. Tacrolimus inhibits calcineurin, and therefore T-cell proliferation, by arresting the cell cycle between G 0 and G 1 in a similar manner to ciclosporin. Tacrolimus is metabolised by the enzyme CYP3A4

Therapeutic indications:

* Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
* Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

**Interactions and cautions**

Tacrolimus is metabolised by the enzyme CYP3A4.

|  |  |
| --- | --- |
| **Increase** Tacrolimus levels | **Decrease** Tacrolimus levels |
| Erythromycin | Carbamazepine |
| Clarithromycin | Phenobarbital |
| Diltiazem | Phenytoin |
| Verapamil | Rifampicin |
| Felodipine | Orlistat |
| Fluconazole, Itraconazole, Ketoconazole | St John’s Wort |
| Grapefruit / pomegranate |  |

Table1: Common medications that interact with tacrolimus. There are other agents that can interact (see BNF interaction checker for full list)(1)(2)

Tacrolimus may cause hyperkalaemia therefore potassium-sparing diuretics should only be initiated with regular monitoring of U&Es.

Tacrolimus may increase levels of dabigatran. Manufacturer does not recommend concomitant use of both drugs.

Tacrolimus may reduce the clearance of steroid-based contraceptives resulting in increased hormone exposure.

Avoid live vaccines.

**Adverse effects**

Some of the common or very common side effects: skin reactions, increased risk of infection, hypertension, headache, sleep disorders, visual disturbances, alopecia, hyperglycaemia and renal impairment(1). For a full list of possible side effects refer to the BNF at *www.bnf.nice.org.uk/drug* or the Summary of Product Characteristics (SPC) at [*www.medicines.org.uk/emc*](http://www.medicines.org.uk/emc)*.*

**Monitoring**

Blood trough tacrolimus levels should be taken 12 hours post-dose, just prior to next dose.

Tacrolimus target levels for renal transplant patients varies on an individual basis depending on date of surgery and other immunosuppression prescribed – discuss with the renal team for each individual patient.

Tacrolimus levels for non-renal transplant indication might differ – discuss with the renal team for each individual patient.

When switching between formulations trough level should be taken before conversion and 3 days post switch.

When administering IV, monitoring should include steady state levels and any required dose adjustment should be led by the renal consultant on call (via switchboard). If the IV tacrolimus is to continue for longer than 5 days weekly steady state levels are recommended. Blood sample must be taken from the opposite site to where the tacrolimus is infused.

Levels above 20 ng/mL may be associated with toxicity. Signs and symptoms of toxicity include tremor, headache, nausea and vomiting, lethargy, increased blood nitrogen and elevated creatinine.

**MHRA warning**

Inadvertent switching between oral tacrolimus products has been associated with reports of toxicity and graft rejection. Prescribe and dispense as brand specific products. To ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only(2).

**Prescribing**

As per Trust policy, Tacrolimus should only be prescribed by doctors who are Registrars level or above or Non-Medical Prescribers if within their scope of practice.

**Tacrolimus administration options for NBM patients**



**NG administration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| PO formulation | Formulation for NG switch | Conversion factor | Instructions | Additional information and cautions |
| Adoport i*mmediate release capsules*  OR  Prograf  *Immediate release capsules* | **Adoport** immediate release capsules (licensed)  OR  **Prograf** immediate release capsules (licensed) | 1:1 | 1. Flush the enteral tube with 30mL of water; 2. Open the Adoport/Prograf capsule and mix with 15-30mL of water; 3. Administer the suspension via the NG tube; 4. Flush the NG tube with 30mL of water if tacrolimus is the last medication administered or 10mL before administering other medications. | Medical staff handling this medicine should wear gloves and a mask to avoid exposure to the medicine powder.  Always use an enteral syringe.  Tacrolimus is absorbed by PVC plastics. Tubing, syringes and any other equipment used should be made of non-PVC material. |
| Modigraf *granules for immediate release suspension* | **Modigraf** granules for immediate release suspension (licensed) | 1:1 | 1. Flush the enteral tube with 30mL of water; 2. Add the granules to a small amount of water (2mL of water for each 1mg of tacrolimus) and stir to mix. 3. Administer the suspension via the NG tube; 4. Flush the NG tube with 30mL of water if tacrolimus is the last medication administered or 10mL before administering other medications. | Medical staff handling this medicine should wear gloves and a mask to avoid exposure to the medicine powder.  Always use an enteral syringe.  Tacrolimus is absorbed by PVC plastics. Tubing, syringes and any other equipment used should be made of non-PVC material. |
| Advagraf *modified released capsules* | **Adoport** immediate release capsules | Total daily dose to 2 divided doses (10am and 10pm) | Refer to Adoport section | Refer to Adoport section.  **Modified release capsules MUST NOT be opened.**  If the doses cannot not be split equally due to capsule size, administer higher dose in the morning (i.e. 1mg OM and 0.5mg ON) |

Avoid administration with high-fat enteral feeds as absorption of tacrolimus might be reduced. To maximise absorption doses should be administered 1 hour before a feed is started or 2 hours after stopping a feed. If a feed break cannot be given the nutrition team should be contacted.

**IV Administration**

**Conversion**

When converting from PO tacrolimus (any brand):

Dose of IV Tacrolimus infusion to be given over 24 hours = **0.2** x PO total daily dose

**Intravenous Infusion**

Ampoules for dilution contain tacrolimus 5mg in 1mL. The diluted solution should not be given as a bolus.

IV infusion: Dilute and give over 24 hours using an infusion pump.

**Diluent**

Dilute in either glucose 5% or sodium chloride 0.9%

**Instructions for dilution**

Total volume should be between 20-500mL. Diluted solution should be transparent and colourless. (4) Intravenous therapy should not be continued for more than 7 days. (5)

When glucose is used as the diluent the infusion has a low pH and may cause venous irritation and tissue damage in cases of extravasation. If a central venous access device is unavailable, administer via a large peripheral vein monitoring insertion site closely.

Tacrolimus is absorbed by PVC plastics. Tubing, syringes and any other equipment used should be made of non-PVC material.

**Rate of administration and expiry**

Final solution must have a concentration within the range of 4–100micrograms/mL.

Expiry date to write on continuous infusion is 24 hours. Store below 25o and protect from light.

**Flush**

Flush with sodium chloride 0.9% or glucose 5%.

**Caution**

Extravasation may cause tissue damage due to the low pH of the solution.

**Extra information**

Switch back to the usual oral dose and form as soon as patient is no longer NBM.

**Conversion from oral to IV switch**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Daily total oral dose** | **Equivalent IV daily dose** | **Amount of IV tacrolimus 5mg/mL** | **Final concentration** | **Rate (mL/hr) = micrograms/Hr** |
| 1mg | 0.2mg | 0.04mL | 4.2 micrograms/mL in 48mL | 2mL/hour = 8.4micrograms/hour |
| 1.5mg | 0.3mg | 0.06mL | 6.25 micrograms/mL in 48mL | 2mL/hour = 12.5micrograms/hour |
| 2mg | 0.4mg | 0.08mL | 8.3 micrograms/mL in 48mL | 2mL/hour = 16.6micrograms/hour |
| 2.5mg | 0.5mg | 0.1mL | 10.4 micrograms/mL in 48mL | 2mL/hour = 20.8micrograms/hour |
| 3mg | 0.6mg | 0.12mL | 12.5 micrograms/mL in 48mL | 2mL/hour = 25micrograms/hour |
| 3.5mg | 0.7mg | 0.14mL | 14.6 micrograms/mL in 48mL | 2mL/hour = 29.2micrograms/hour |
| 4mg | 0.8mg | 0.16mL | 16.7 micrograms/mL in 48mL | 2mL/hour = 33.4micrograms/hour |
| 4.5mg | 0.9mg | 0.18mL | 18.75 micrograms/mL in 48mL | 2mL/hour = 37.5micrograms/hour |
| 5mg | 1.0mg | 0.2mL | 20.8 micrograms/mL in 48mL | 2mL/hour = 42micrograms/hour |
| 5.5mg | 1.1mg | 0.22mL | 22.9 micrograms/mL in 48mL | 2mL/hour = 45.8micrograms/hour |
| 6mg | 1.2mg | 0.24mL | 25 micrograms/mL in 48mL | 2mL/hour =50micrograms/hour |
| 6.5mg | 1.3mg | 0.26mL | 27.1 micrograms/mL in 48mL | 2mL/hour =54.2micrograms/hour |
| 7mg | 1.4mg | 0.28mL | 29.2 micrograms/mL in 48mL | 2mL/hour =58.4micrograms/hour |
| 7.5mg | 1.5mg | 0.3mL | 31.25 micrograms/mL in 48mL | 2mL/hour =62.5micrograms/hour |
| 8mg | 1.6mg | 0.32mL | 33.3 micrograms/mL in 48mL | 2mL/hour = 66.6micrograms/hour |

*Intravenous doses between 0.2 and 4.8mg/day may be diluted to 48mL, giving a final concentration range of 4 to 100microgams/mL. Doses outside those ranges might require a different volume of diluent to ensure adequate concentration.*

For doses outside of the above chart follow the example calculation below

**Example calculation**

1. **Calculate amount of IV tacrolimus required depending on patients total daily dose;**

E.g. patient takes 12mg total orally a day

12 mg x 0.2 = 2.4mg IV equivalent

1. **Volume of IV tacrolimus required;**

Vials of 5mg in 1mL solution are available for dilution.

2.4mg divided by 5mg = 0.48ml of the 5mg/ml solution

1. **Calculate final concentration of solution using diluent; Dose diluted to 48 mL;**

E.g. 2.4mg in 48 mL; equivalent to 2400micrograms in 48 mL = 50micrograms per mL

1. **Calculate rate of administration;**

Rate of tacrolimus administration is 2ml per hour:

50 micrograms x 2 = 100 micrograms per hour (3).

**References**

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